REMARKS

The Office Action of September 25, 2006 has been carefully considered. Claims 1-3 and 17 have been amended to further clarify the nature of the claimed subject matter as a method for drug screenings, not a method for studying the three-dimensional structure of the PDZ domain of postsynaptic density-95 protein. Support to the amendment can be found throughout the original specification (e.g., paragraphs [0001], [0004], [0009] and [0028]). Claims 18-22 are amended to correct a typographic error. No new matter is therefore introduced.

Applicants' remarks are as follows:

The Present Invention and the Tubiash Reference

The Present Invention:

The subject matter of the present invention is a method of screening for chemical compounds potentially useful as neuroprotective drugs. According to the present invention, NMR spectroscopy is used as an efficient and effective screening method for identifying compounds that interact with the PDZ domain of PSD-95. As amended, the method comprises 7 specific elements: a) obtaining a sample of free Postsynaptic density-95 protein; b) taking a first NMR spectrum of the free PDZ domain of said free Postsynaptic density-95 protein; c) adding a test compound into said sample of free Postsynaptic density-95 protein to form a test sample; d) incubating said test compound with said PDZ domain to allow binding reaction; e) taking a second NMR spectrum of said incubated PDZ domain; f) making a comparison between comparing said first and second NMR spectra; and g) making an assessment about said test compound's potential as a neuroprotective drug based on said comparison.

The Tochio Reference:

The Tochio reference, the inventors' own prior scientific publication, is a report about determination of the three-dimensional structure of PDZ-2 (the second PDZ domain of PSD-95) and backbone dynamics of the structure in solution. In that report, the inventors used CAPON, a peptide **known** to be able to competitively dissociate the interaction between of PSD-95 and nNOS, to understand the location and the nature of the recognition site in the

PDZ domain of PSD95 in light of the newly developed 3-D structure model. Based on the changes in NMR spectrum while **titrating ^{15}N-labed PDZ-2 with CAPON**, the inventors concluded that "the CAPON peptide can indeed bind to the expected peptide-binding groove located between αB and βB. The peptide-binding-induced conformational changes are particularly obvious in the GLGF loop and the αB/βF loop of PSD-95 PDZ2."

While the inventors' previous findings disclosed in the Tochio reference provided part of the basis for the present invention, it neither taught nor suggested anything about the drug screen method of the present invention.

Claim Rejections – 35 USC § 102

The Examiner rejected claims 1-3, 16-19, 21, and 22 under 35 U.S.C. 102(b) as being anticipated by the Tochio reference. This rejection is erroneous both in fact and in law. Factually, the Examiner asserted that "Tochio et al teach a method of testing the effect of a potential binding partner of PDZ2 of PSD-95." This is a mischaracterization of the reference because the Tochio reference never tested the effect of a potential binding partner of PDZ2 of PSD-95. The only binding partner used in the reference was a portion of CAPON. However, CAPON was a **known** competitive antagonist in the binding between nNOS and PSD-95 ("Biochemical studies showed that CAPON can competitively dissociate the PDZ/PDZ interaction between nNOS and PSD-95," page 227 of the Tochio reference). It was not a potential antagonist as erroneously suggested by the Examiner. The Tochio reference used **a known antagonist** to further characterize the binding site in terms of the newly developed the 3-D structure model of the PDZ domain, and it disclosed no method for determining whether CAPON was a antagonist, much less a method of screening for potential neuroprotective drugs.

Because the Tochio reference and the present invention were about different methods (using known antagonist in studying binding site in the PDZ domain vs. using the NMR spectra pattern changes in screening for antagonists as potential neuroprotective drugs), it is no surprise that they call for different steps. For examples, the Tochio reference needed a step "**titrating** titrate ^{15}N-labeled PSD-95 PDZ2" with a CAPON peptide of 12 residues, while claim 1 of the present application recites a step of comparing NMR spectra **taken before and after** incubating PDZ with a small molecule compound. Clearly, as a matter of fact, the

Tochio reference cannot be used as a section 102 reference against the present invention. The rejection based on said reference is thus improper.

The rejection made under 35 U.S.C. section 102 is also improper as a matter of law. The Examiner made the rejection based on mere overall assertions about the claimed subject matter and the Tochio reference, rather than a thorough analysis based on an element-by-element comparison, as repeatedly required by the court. As such, no *prima facie* case of anticipation has been made, and the rejection based thereupon must be set aside.

The Examiner's attention is respectfully directed to the law of anticipation as set forth by the Federal Circuit to ensure the rejection and our response to be guided by proper legal standards for anticipation:

> An anticipating reference must describe the patented subject matter with **sufficient clarity and detail to establish that the subject matter existed** and that its existence was recognized by persons of ordinary skill in the field of the invention.

ATD Corp. v. Lydall, Inc., 48 USPQ 2d 1321, 1328 (Fed. Cir. 1998) (emphasis added).

> Anticipation requires the presence in a single prior art reference disclosure of **each and every element** of the claimed invention, arranged as in the claim."

Lindemann Maschinenfabrik v. American Hoist & Derrick Co., 221 USPQ 481, 485 (Fed. Cir. 1984) (emphasis added).

To apply the above law of anticipation, it is respectfully submitted that in order to make the rejection the Examiner must identify in the Tochio reference each and every element recited in the rejected claims. Specifically, each of the rejected claims recites the following limitations:

a) a step of obtaining a sample of free Postsynaptic density-95 protein;

b) a step of taking a first NMR spectrum of the free PDZ domain of said free Postsynaptic density-95 protein;

c) a step of adding a test compound into said sample of free Postsynaptic density-95 protein to form a test sample;

d) a step of incubating said test compound with said PDZ domain to allow binding reaction;

e) a step of taking a second NMR spectrum of said incubated PDZ domain;

f) a step of making a comparison between comparing said first and second NMR spectra; and

g) a step of making an assessment about said test compound's potential as a neuroprotective drug based on said comparison.

Therefore, for maintaining a section 102 rejection, the Examiner must identify each and every of the above steps in the Tochio reference, and those steps must also be performed in the same order as recited in the rejected claims.

Claim Rejections – 35 USC § 103

The Examiner rejected claims 1-9, 12- 22 under 35 U.S.C. 103 as being unpatentable over Tochio et al in view of Lee et al (Neuroscience Lett, 2000) and Aarts et al (Science, 2002). Again, the rejection was made based on overall assertions about the claimed subject matter and the prior art references, and made no reference to the specific limitations recited in the rejected claims. As detailed above, each of the rejected claims recites at least seven limitations (i.e., step (a) to step (g)). It is unclear from the Office Action how each of the cited prior art references relates to the limitations recited in the claims under rejection. Thus, no *prima facie* case under section 103 was made. For example, claim 1 was rejected under section 103 over Tochio in view of Lee because the Examiner believed Lee supplied information about flavonoids which was missing from Tochio. However, flavonoids are simply irrelevant to claim 1. Claim 1 does not even mention flavonoids.

Applicant respectfully submits that none of the prior art references cited by the Examiner, alone or in combination, teaches or renders obvious the claimed subject matter of the present application and rejection of the claims based on those references is far-fetched and improper.

Conclusion

In view of the foregoing remarks, Applicant respectively submits that the present invention is neither anticipated by Tochio et al. nor rendered obvious by Tochio et al. in view

of Lee et al and/or Aarts et al. Reconsideration and allowance of the application are earnestly solicited.

It is believed that no additional fees and charges are required at this time in connection with the application.

Respectfully submitted,

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